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**BY COURIER**

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Rockville, MD 20852

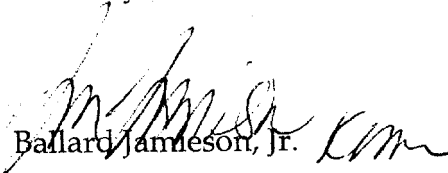
**Re: Docket No. 97N-0023**

Dear Sir or Madam:

Please find enclosed two originals and one copy of The International Pharmaceutical Aerosol Consortium's ("WAC") comments in response to the FDA's Notice of Proposed Rulemaking entitled *Use of Ozone-Depleting Substances; Essential Use Determinations*, dated September 1, 1999. Please file the original copies and time/date stamp the photocopy and return it to the messenger.

Thank you for your consideration.

Sincerely,

  
Ballard Jamieson, Jr.

Enclosure

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97N-0023

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# IPAC

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INTERNATIONAL PHARMACEUTICAL AEROSOL CONSORTIUM

**IPAC Comments on  
Notice of Proposed Rulemaking Governing  
Use of Ozone-Depleting Substances and  
Essential Use Determinations**

**(64 Fed. Reg. 47719, September 1, 1999)**

November 30, 1999

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**November 30, 1999**

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## TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	COMMENTS ON THE PROPOSED RULE.....	2
	A. Essential Use Determinations.....	2
	<i>Moiety-By-Moiety Approach</i> .....	2
	<i>Criteria for Alternatives</i> .....	2
	<i>Same Route of Administration</i> .....	2
	<i>Same Indication</i> .....	3
	<i>Same Level of Convenience</i> .....	3
	<i>Levels Sufficient to Meet Patient Need</i> .....	4
	<i>One Year of U.S. Postmarketing Data</i> .....	4
	<i>Patients...are Adequately Served</i> .....	5
	<i>Determinations After 2005</i> .....	5
	B. New CFC MDI Products.....	6
	C. Nasal Products.....	7
III.	CONCLUSION.....	8

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# I

## INTRODUCTION

The International Pharmaceutical Aerosol Consortium (IPAC) is an association of leading manufacturers of metered dose inhalers (MDIs) for the treatment of asthma and chronic obstructive pulmonary disease. Its members are both research-based and generic, and include: AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Glaxo Wellcome, Medeva Americas, Inc., Norton Healthcare Ltd., Rhône-Poulenc Rorer, Inc., and 3-M Pharmaceuticals.

IPAC was created in response to the mandate of the Montreal Protocol. IPAC's goal is to ensure a smooth and efficient MDI transition that balances public health and environmental protection. To this end, IPAC serves as a source of information and analysis on the MDI industry and coordinates its participation in the implementation of the Protocol worldwide.

Members of IPAC are firmly committed to the MDI transition. In 1990, MDI companies undertook an unprecedented joint testing program to demonstrate the safety of propellants that would ultimately replace CFCs. More than 1400 scientists, at 90 laboratories, in 10 countries have been involved in the development of non-CFC MDIs. MDI companies have already spent more than \$1 billion dollars in this effort and will need to spend even more to complete it.

In May 1997 IPAC submitted comments on the Advance Notice of Proposed Rulemaking entitled *Chlorofluorocarbon Propellants in Self Pressurized Containers; Determinations That Uses are No Longer Essential; Request for Comments* (62 Fed. Reg. 10242, March 6, 1997) (ANPRM). On April 11, 1997 IPAC presented its views on the ANPRM at the public hearing of the Pulmonary-Allergy Drugs Advisory Committee.

These comments are submitted in response to the Notice of Proposed Rulemaking entitled *Use of Ozone-Depleting Substances; Essential Use Determinations* (64 Fed. Reg. 47719, September 1, 1999) ("Proposed Rule"). IPAC also commented on the Proposed Rule at the public hearing of the Pulmonary-Allergy Drugs Advisory Committee on November 22, 1999. While these comments reflect the views of all members of IPAC, several members will separately submit comments supplementing these comments.

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## II

### COMMENTS ON THE PROPOSED RULE

#### A. Essential Use Determinations

##### **MOIETY-BY-MOIETY** *APPROACH*

**The** Proposed Rule provides for a moiety-by-moiety approach for determining whether an MDI product remains essential (Proposed Rule, §2.125(g)(3)(i)).

IPAC supports consideration of active moieties in determining whether a product is essential. It strikes an appropriate balance between ensuring the availability of vital medications and discontinuing the use of CFCs.

##### *CRITERIA FOR ALTERNATIVES*

The Proposed Rule establishes the following criteria for an alternative to a CFC MDI:

##### *“Same Route **of** Administration”*

The Proposed Rule provides that a product must feature the “same route of administration” in order to qualify as an alternative to a CFC MDI (Proposed Rule, §2.125(g)(3)(i) and (g)(4)(i)).

IPAC supports this criterion. Inhalation is the preferred route of administration for the treatment of respiratory disease. To ensure the continued availability of inhalation therapy, a CFC MDI should only be replaced by a product with the “same route of administration.”

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The Proposed Rule provides that a product must treat “the same indication” in order to qualify as an alternative to a CFC MDI (Proposed Rule, §2.125(g)(3)(i) and (g)(4)(i)). For example, a product for the treatment of adults only would not qualify as an alternative to a CFC MDI indicated for the treatment of both adults and children (Preamble, 64 Fed. Reg. at 47725).

IPAC supports this criterion. This criterion ensures that patients will have alternative non-CFC products for the treatment of the same indications currently treated with CFC MDIs.

*“Same Level of Convenience”*

The Proposed Rule provides that a product must feature “approximately the same level of convenience of use” in order to qualify as an alternative to a CFC MDI (Proposed Rule, §2.125(g)(3)(i) and (g)(4)(i)). Under this criterion, the FDA would consider whether an alternative had “approximately the same or better portability” and “the same amount of or less preparation before use” (Preamble, 64 Fed. Reg. at 47722). For example, the FDA would not regard “an air-pressure driven nonportable nebulizer” as an alternative to a CFC-MDI because of its “lack of portability and ease of use” (Preamble, 64 Fed. Reg. at 47726).

IPAC supports this criterion. As the FDA notes, “patients value the compact size and ease of use of MDIs” (Preamble, 64 Fed. Reg. at 47722). This criterion ensures continuing patient access to therapy with this “same level of convenience.”

We recognize, however, that any general criterion of this kind could be subject to overly broad interpretations. For example, the phrase “level of convenience” could possibly be construed to include inconsequential matters of personal preference regarding minor variations in size, shape, color, and taste of medication. To ensure that otherwise acceptable non-CFC alternatives are not unreasonably disqualified under this criterion, the FDA should confirm that only significant variations in convenience which materially impede patient compliance are a basis for disqualification under the Proposed Rule.

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*“Levels Sufficient to Meet Patient Need”*

The Proposed Rule states that “supplies and production capacity” for a non-CFC alternative must “exist or will exist at levels sufficient to meet patient need” (Proposed Rule, §2.125(g)(3)(ii)).

IPAC supports this criterion. This criterion would safeguard against interruptions in patient access to vital medications during the transition to non-CFC MDIs.

In the Preamble to the Proposed Rule, the FDA states that a non-CFC alternative should be “manufactured at multiple manufacturing sites if the [CFC MDI] was manufactured at multiple manufacturing sites” (Preamble, 64 Fed. Reg. at 47723).

IPAC believes that the requirement of multiple manufacturing sites is unnecessary unless FDA determines that a single manufacturing site is not “sufficient to supply patient need.” MDI companies may consolidate manufacturing activities at a single site for non-CFC MDIs. These single sites will feature supplies, storage, and production capacities, as well as safeguards against disruptions in manufacture, which virtually eliminate risk of product shortages.

*“One Year **of** U.S. Postmarketing Data”*

Under the Proposed Rule, the FDA would require “at least one year of U.S. postmarketing use data” for non- CFC alternatives (Proposed Rule, §2.125(g)(3)(iii)). In particular, the FDA would review information on:

device performance in uncontrolled settings, tolerability of products in widespread use, unusual adverse reactions not previously identified in premarketing studies, and effectiveness in broader patient populations (Preamble, 64 Fed. Reg. at 47723).

In addition, the FDA would consider “foreign data supportive of U.S. postmarketing use data if U.S. and foreign formulations, patient populations, and clinical practices were the same or substantially similar” (Preamble, 64 Fed. Reg. at 47723). Finally, the FDA would “not require a postmarketing study if available data, including more traditional postmarketing surveillance data, are sufficient to support a finding that the CFC product is no longer essential” (Preamble, 64 Fed. Reg. at 47730).

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IPAC supports this criterion, with the following clarification. IPAC does not support Phase-IV studies in the post-marketing period. In addition, IPAC proposes that the requirement for one year of postmarketing use data in the United States be reduced if foreign postmarketing use data is sufficient to support a finding that a CFC MDI is no longer essential. This approach would eliminate unnecessary delay in discontinuing the use of CFCs.

*“Patients...are Adequately Served”*

Under the Proposed Rule, the FDA would determine whether patients who rely on a particular CFC MDI would be “adequately served” by non-CFC alternative(s) to that product (Proposed Rule, §2.125(g)(3)(iv)). In making this determination, the FDA would consider whether “adequate safety, tolerability, effectiveness, and compliance exist for the indicated populations and other populations known to medically rely” on the CFC MDI product.

IPAC supports this criterion. This criterion ensures that vital medications will remain available as long as necessary for all clinical subpopulations.

**DETERMINATIONS AFTER 2005**

The Proposed Rule provides that after January 1, 2005, a CFC MDI will no longer be essential unless it provides “an unavailable important public health benefit” which warrants the release of CFCs into the atmosphere. This determination would be made by a notice-and-comment rulemaking after consultation with a relevant FDA advisory committee(s) and an open public meeting (Proposed Rule, §2.125(g)(2) and §2.125(f)).

IPAC supports a target date for commencing the final phase of the transition to non-CFC alternatives that would give physicians and patients a general sense of the timeframe for its completion.

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## B. New CFC MDI Products

Under the Proposed Rule, any petition to add an essential use to Section 2.125(e) would have to include compelling evidence that the new CFC MDI product would “provide an unavailable important public health benefit” (Proposed Rule, §2.125(f)). According to the FDA, it would be “inappropriate” to add such uses except in “extraordinary circumstances” in view of the phaseout of CFC MDIs. By contrast, however, any new CFC MDI containing a moiety already found in §2.125(e) would automatically be considered essential under the Proposed Rule even if it did not provide an unavailable important public health benefit.

As early as 1996, the Technology and Economic Assessment Panel of the Montreal Protocol observed that the “introduction of new CFC-containing MDIs is a serious impediment to the expeditious phaseout of CFCs from MDIs” (June 1996 TEAP Report, p.109). For this reason, the American Lung Association, the American Thoracic Society, the Asthma and Allergy Foundation of America, the Cystic Fibrosis Foundation and other leading public health organizations have urged the 11th Meeting of the Parties to the Montreal Protocol to disallow CFCs for new MDIs unless they fulfill an unmet medical need. In addition, leading members of the United States Congress have urged the United States to support such action at the 11th Meeting.

Unfortunately, the FDA’s Proposed Rule does not adopt this approach. The FDA has apparently concluded that it should determine that any new CFC MDI product is essential even where the new product does not provide an unavailable important public health benefit.

Under §601(8)(B) of the Clean Air Act, however, the Commissioner of the Food and Drug Administration, in consultation with the Administrator of the Environmental Protection Agency, is authorized to determine whether any new CFC MDI “product” is “essential.” Section 604(d)(2) of the Act authorizes CFCs for MDIs, but only to the extent “consistent with the Montreal Protocol.” Under the Montreal Protocol, the use of CFCs in a new MDI product is essential only if the new CFC MDI “product” is “necessary for the health...of society” (Decision IV/25). Thus, the FDA must determine on a product-by-product basis that any new CFC MDI is not essential under the Montreal Protocol and the Clean Air Act where it does not provide an unavailable important public health benefit.

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IPAC requests that the FDA amend its Proposed Rule to provide that, regardless of the moieties they may contain, all new CFC MDIs not covered by approved marketing applications as of the effective date of the Final Rule, will only be found essential if they provide an “unavailable important public health benefit.” An amendment of this kind would facilitate the MDI transition without risk to public health.

## C. Nasal Products

Metered-dose steroid human drugs for nasal inhalation are considered nonessential by the Parties to the Montreal Protocol. The Proposed Rule would remove the essential use designation for these products in the United States (Preamble, 64 Fed. Reg. at 47721). IPAC supports this decision.

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# III

## CONCLUSION

IPAC submits these Comments on the Proposed Rule in the interests of patient care and environmental protection. IPAC will participate actively in this and other proceedings on the transition to non-CFC MDIs.